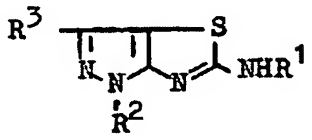
2-Amino-pyrazolo[3,4-d] thiazoles

The invention relates to compounds of formula I



I,

in which

R^1 signifies hydrogen, optionally substituted alkyl, cycloalkyl, aralkyl, aryl, acyl or sulfonyl,

R^2 signifies optionally substituted alkyl, cycloalkyl, aralkyl, aryl or heteroaryl and

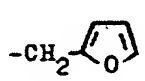
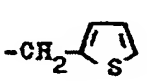
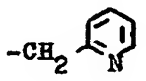
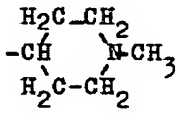
R^3 signifies hydrogen, alkyl with 1 to 4 C-atoms, or optionally substituted phenyl, as well as a process for the production of these compounds.

Examples that may be mentioned in particular for R^1, apart from hydrogen, are alkyl with 1 to 8 C-atoms, cyclohexyl, phenylalkyl with a total of 7 to 10 C-atoms, substituted phenyl, alkanoyl, aralkanoyl, alkoxy- or aroxycarbonyl, aroyl, alkylsulfonyl and arylsulfonyl, whereby the radicals contain 1 to 12 C-atoms, preferably 1 to 8 C-atoms.

Individual radicals R^1, apart from those already mentioned, are for example methyl, ethyl, propyl, butyl, amyl, β-ethylhexyl, benzyl, phenylethyl, -propyl or -butyl, hexyl, phenyl, phenyl substituted by chlorine, bromine, methyl, ethyl, methoxy, ethoxy or nitro; also acetyl, propionyl, butyryl, caproyl, hexanoyl, capryloyl, chloroacetyl, bromoacetyl, α-chloropropionyl, β-chloropropionyl, γ-chloro-n-butyryl, α-bromoisovaleroyl, phenylacetyl, tolylacetyl, methoxyphenylacetyl, chlorophenylacetyl, dichlorophenylacetyl, methoxycarbonyl, ethoxy-, propoxy-, butoxy- or phenoxycarbonyl, benzoyl, benzoyl substituted by chlorine, bromine, nitro, methoxy, ethoxy or methyl; methylsulfonyl, ethyl-, propyl-, butyl-, cyclohexyl-, benzyl-, phenylethyl-, phenyl-, chlorophenyl-, dichlorophenyl-, methylphenyl-, dimethylphenyl- or thienylsulfonyl.

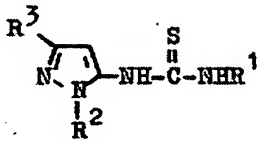
Examples of radicals R^2 which may be mentioned are alkyl with 1 to 4 C-atoms, cyclopentyl, cyclohexyl, optionally substituted benzyl, phenylethyl and substituted phenyl. Apart from those already mentioned, individual radicals are, for example, methyl, ethyl, propyl, butyl, β-cyanoethyl, β-hydroxyethyl, methoxypropyl, benzyl substituted by chlorine, bromine, methyl,

dimethylamino or methoxy; phenyl, phenyl substituted by chlorine, bromine, methyl, ethyl, methoxy, ethoxy, nitro or cyano, as well as the radicals of formulae

Individual radicals R^3 are, for example, hydrogen, methyl, ethyl, phenyl or phenyl substituted by chlorine, bromine, nitro, methyl, ethyl, methoxy or ethoxy.

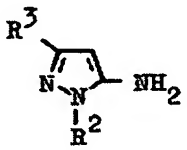
In order to produce compounds of formula I, compounds of formula II



II,

undergo cyclisation under dehydrating conditions.

Compounds of formula II are readily obtainable, for example by reacting compounds of formula III



III

with compounds of formula IV

R^1-NCS IV.

Compounds of formulae III and IV are known, and their preparation is described, for example, in the following literature:

Compounds of formula III:

a) DTOS 2 141 700

b) H. Höhn, Z. Chem. 10. 386 - 388 (1970)

Compounds of formula IV:

a) DAS 1 183 492

b) Houben-Weyl, Methoden der organischen Chemie, 4 edition, vol. 9, p. 879, G. Thieme, Stuttgart, 1955

c) P. A. S. Smith, R. O. Kan; J. Org. Chemistry 29 2261 (1964)

d) R. Pohoudek-Fabini, E. Schröpl; Pharmazeutische Zentralhalle 107. 277 (1968)

Cyclisation of the compounds of formula II is suitably carried out in a solvent or suspension agent at temperatures from -5 to 150°C, preferably from 0 to 80°C.

Suitable dehydration agents are all those that are conventionally used in the so-called Hugershoff reaction (R. C. Elderfield, Heterocyclic Compounds, Vol. 5, page 512 and page 581). Chlorine, sulfuryl chloride, disulfur dichloride and, in particular, bromine, may be named individually.

The following are examples of solvents and/or suspension agents: water, halogen-containing hydrocarbons, lower fatty acid esters, lower fatty acids or mineral acids. The following may be mentioned individually as suitable reaction media: ethyl acetate, dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, nitrobenzene, formic acid, acetic acid, propionic acid, hydrochloric acid or sulfuric acid.

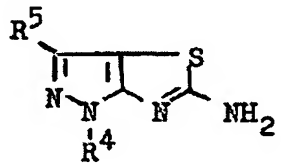
To carry out the process, the compound of formula II is conveniently dissolved or suspended in the solvent employed, and then the oxidation or dehydration agent is added. It is advantageous for the reaction mixture to be stirred and cooled, if required, or to heat briefly after an initially exothermic reaction has died down. As a rule, approximately two equivalents of the dehydration agent are used per equivalent of thiourea.

Working up depends on the dehydration agents and solvents employed. Frequently, the 2-amino-pyrazolo[3,4-d]thiazoles or corresponding salts that are formed may crystallise during the reaction, in which case they may be isolated, e.g. by filtering or centrifuging.

From the salts, the free amines are obtained by dissolution or suspension in water or in an organic solvent, adding for example caustic soda solution, caustic potash solution, aqueous ammonia, sodium carbonate or potash.

A simplification of the process is to produce the end products of formula I directly in a type of one-pot reaction without isolating the intermediates of formula II obtained from compounds III and IV.

Compounds of formula Ia are of particular significance



Ia,

in which

R^4 signifies alkyl with 1 to 4 C-atoms, cyclohexyl, benzyl, phenyl or chlorophenyl, and

R^5 signifies hydrogen or allyl with 1 to 4 C-atoms.

The new 2-amino-pyrazolo[3,4-d]thiazoles are valuable starting materials for the production of dyestuffs, whereby they serve as diazo components.

The parts indicated in the examples are parts by weight. They are related to parts by volume as kilograms to liters.

Example 1

2-ethoxycarbonylamino-6-butyl-pyrazolo[3,4-d]thiazole

8 parts of bromine are added dropwise, whilst stirring, to 13.5 parts of N-(1-butyl-pyrazolyl-5)-N'-carbethoxy-thiourea in 80 parts of chloroform, whereby the temperature rises to 30°C. When this addition is complete, heating is effected for ½ hour to 40°C, after which stirring is effected for 3 hours at room temperature. The chloroform is distilled off under reduced pressure and the oily residue is taken up in alcohol. After adding water and a little ammonia, the free base precipitates.

Yield: 7.8 parts (58%)

A sample recrystallised from ethanol/water melts at 168-170°C.

analysis:	$C_{11}H_{16}N_4O_2S$ (268,27)
calc:	C 49,25 H 6,01 N 20,
found:	49,5 6,0 21,

Example 2

2-ethoxycarbonylamino-6-butyl-pyrazolo[3,4-d]thiazole

A solution of 16 parts of bromine in 20 parts of glacial acetic acid is added dropwise, whilst stirring, to 13.5 parts of N-(1-butyl-pyrazolyl-5-)N-carbethoxythiourea in 80 parts of glacial acetic acid. A solid is temporarily formed, but dissolves again. After standing at room temperature for 15 hours, the mixture is precipitated with 200 parts of water, filtered by suction and dried in a vacuum at 50°C. Yield: 9.7 parts (75%). A sample recrystallised from ethanol/water melts at 168-170°C.

Example 3

2-ethoxycarbonylamino-6-cyclohexyl-pyrazolo[3,4-d]thiazole

7.4 parts of N-(1-cyclohexyl-pyrazolyl-5-)N'-carbethoxythiourea are dissolved in 60 parts of glacial acetic acid, and 8 parts of bromine in 10 parts of glacial acetic acid are added, whilst stirring. After stirring for 2 hours, the mixture is poured into 300 parts of water, the solid is filtered by suction and dried in a vacuum at 50°C.
Yield: 6.9 g (94%); A sample recrystallised from ethanol/water melts at 182-184 °C.

Analysis:	$C_{13}H_{18}N_4O_2S$ (294,31)				
calc.:	53,05	H 6,16	N 19,04	O 10,88	S 10,88
found:	52,9	6,3	18,7	10,9	10,5

Example 4

2-benzoylamino-6-cyclohexyl-pyrazolo[3,4-d]thiazole

16 parts of bromine, dissolved in 10 parts of glacial acetic acid, are added slowly whilst stirring to 16.4 parts of N-(1-cyclohexyl-pyrazolyl-5-)N'-benzoyl-thiourea in 80 parts of glacial acetic acid. The temperature is maintained between 0 and 10°C. Part of the suspension goes into solution at first, but then separates again as an oil. After adding 70 parts of chloroform and stirring for 2 hours, filtration by suction takes place, and the partly oily residue is dissolved in 100 parts of dimethylformamide and precipitated with aqueous ammonia.
Yield: 12 parts (73%);
A sample recrystallised from alcohol and water melts at 187-89°C.

Analysis:	$C_{17}H_{18}N_4OS$ (326,35)				
calc.:	C 62,56	H 5,56	N 17,17	O 4,9	S 9,8
found:	62,8	5,7	17,1	5,1	9,5

Example 5

2-ethoxycarbonylamino-6-benzyl-pyrazolo[3,4-d]thiazole

A solution of 16 parts of bromine in 20 parts of glacial acetic acid is added dropwise, whilst stirring, to 15.2 parts of N-(1-benzyl-pyrazolyl-5-)N'-ethoxycarbonyl-thiourea in 100 parts of glacial acetic acid. The temperature is maintained at below 25°C during this addition. When the addition is complete, stirring is effected for 4 hours, and the mixture is then stirred into 500 parts of water. The water is decanted and the partially oily residue is rubbed with a little ethanol and crystallised.
Yield: 9 parts (59%);
A sample recrystallised from alcohol melts at 168-70 °C.

analysis:	$C_{14}H_{14}N_4O_2S$ (302,28)
calc.:	

found:	C55,62	H 4,67	N 18,54	O 10,58	S 10,58
	55,6	5,0	18,4	10,8	10,6

Example 6

2-p-toluenesulfonylamino-6-benzyl-pyrazolo[3,4-d]thiazole

A solution of 8 parts of bromine in 20 parts of glacial acetic acid is added slowly at room temperature to 9.65 parts of N-(1-benzyl-pyrazolyl-5-)N'-p-toluenesulfonyl-thiourea in 100 parts of glacial acetic acid. At first, a solution is formed, and gradually a solid separates. After standing for 24 hours at room temperature, filtration takes place by suction, followed by washing with ether and drying.

Yield: 8.7 parts (91%);

A sample recrystallised from alcohol melts at 192-95 °C.

analysis:	$C_{18}H_{16}N_4O_2S_2$ (384,34)				
calc.:	C 56,25	H 4,20	N 14,58	O 8,33	S 16,66
found:	56,4	4,5	14,5	8,6	16,3

Example 7

2-(p-chlorobenzoyl)amino-6-phenyl-pyrazolo[3.4-d]thiazole

A solution of 8 parts of bromine in 20 parts of glacial acetic acid is added at room temperature to 8.9 parts of N-(1-phenyl-pyrazolyl-5-)N'-p-chlorobenzoyl-thiourea in 60 parts of glacial acetic acid. After stirring for 8 hours, the mixture is stirred into 300 parts of water, filtered by suction and dried.

Yield: 7.8 parts (87%);

A sample recrystallised from methyl glycol melts at 196-200 °C.

analysis:	$C_{17}H_{11}N_4OSCl$ (354,82)
calc.:	Cl 10,00
found:	9,6

Example 8

2-amino-6-cyclohexyl-pyrazolo[3,4-d]thiazole

A solution of 8 parts of bromine in 10 parts of glacial acetic acid is added dropwise at room temperature to 5.6 parts of N-(1-cyclohexyl-pyrazolyl-5-)-thiourea in 50 parts of glacial acetic acid. An oil forms. Upon heating to 80°C, a solution is produced, from which a solid crystallises upon cooling. This is separated, dissolved in 50 parts of dimethylformamide and precipitated again with aqueous ammonia.
Yield; 3.1 parts (56%);
A sample recrystallised from alcohol melts at 205-205 °C.

analysis:	$C_{10}H_{14}N_4S$ (222,24)			
calc.:	C 54,04	H 6,35	N 25,21	S 14,40
found:	53,8	6,1	25,5	14,0

Example 9

2-amino-6-phenyl-pyrazolo[3,4-d]thiazole

4 parts of bromine in 10 parts of glacial acetic acid are added slowly whilst stirring to 5.45 parts of N-(1-phenyl-pyrazolyl-5-)thiourea in 70 parts of glacial acetic acid. When the addition is complete, the mixture is heated for 10 minutes to 80°C, cooled, filtered by suction and washed with water. The residue is dissolved in dimethylformamide and precipitated again by adding aqueous ammonia.

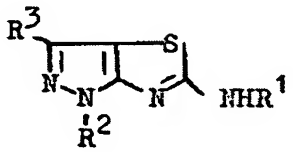
Yield: 3.6 parts (67%);

A sample recrystallised from alcohol melts at 204-206 °C.

analysis:	$C_{10}H_8N_4S$ (216,20)			
calc.:	C 55,55	H 3,73	N 25,92	S 14,80
found:	55,8	3,7	26,0	14,8

What we claim is:

1. 2-Amino-pyrazolo[3,4-d] thiazoles of formula



I

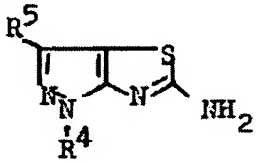
in which

R^1 signifies hydrogen, optionally substituted alkyl, cycloalkyl, aralkyl, aryl, acyl or sulfonyl,

R^2 signifies optionally substituted alkyl, cycloalkyl, aralkyl, aryl or heteroaryl and

R^3 signifies hydrogen, alkyl with 1 to 4 C-atoms, or optionally substituted phenyl.

2. Compounds according to claim 1 of formula



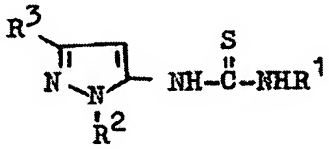
Ia

in which

R^4 signifies alkyl with 1 to 4 C-atoms, cyclohexyl, benzyl, phenyl or chlorophenyl, and

R^5 signifies hydrogen or alkyl with 1 to 4 C-atoms.

3. Process for the production of compounds according to claim 1, characterised in that compounds of formula



undergo cyclisation under dehydrating conditions.